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Solvents effect on the stability and reactivity of Tamoxifen and its nano metabolites as the breast anticancer drug

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ABSTRACT

The effect of protic and aprotic solvents polarity on optimized geometry and some chemical reactivity indices for Tamoxifen (TAM) and three of its important metabolites, i.e. 3-hydroxy Tamoxifen (3-HTAM), Droloxifen, 4-hydroxy Tamoxifen (4-HTAM), Afimoxifen, and *Z*-*N*-desmethyl-4-hydroxy Tamoxifen, Endoxifen (ENDX), antitumor are studied theoretically by density functional theory calculations (B3LYP) with 6-311++G(d, p) basis set in combination with polarizable continuum model (PCM) in selected non polar (CCl_4), polar protic (H_2O, Ethanol) and polar aprotic (DMSO, Acetone) solvents. The solvent-induced stretching vibrational frequency shifts (SFS) and the solvation influence on the DFT based chemical reactivity indices such as atomic charges, HOMO-LUMO energies, stabilization energies, variation of dipole moment of the conformers, ionization potential, electron affinity, chemical potential, hardness and softness have been investigated. The present results show the high kinetic stability and low chemical reactivity of Tam and its important active metabolite, Endoxifen, in water medium. So a drug carrier with good aqueous solubility should be applied to improve the bioavailability of these antitumor drugs.

1. Introduction

Approximately two-third of all breast tumors is estrogen receptor α (ER α) positive and estradiol. The female sex hormone plays remarkable role in the progress and induction of breast cancer [1]. The nonsteroidal antiestrogen Tamoxifen [trans-1-(4-β-desmethylaminoethoxyphenyl)-1,2-diphenylbut-1-ene] is the "gold standard" and widely used drug of (ESRα)-positive breast cancer in pre- and post-menopausal women [2]. Clinical studies showed that TAM therapy could significantly decrease the death rate from the disease [3]. Laboratory studies showed that TAM blocked estrogen binding to ESR [4]. Since TAM is a weak anti estrogen, it undergoes extensive biotransformation to metabolites that have grater antiestrogenic potency in human serum. The binding sites of anticancer drug TAM and its metabolites are located on human serum albumin (HSA). In order to be clinically effective, the prodrug TAM must be converted to ENDX by cytochrome P450 2D6 (CYP2D6). CYP2D6 also converted TAM to 4-HTAM that has 100-fold grater affinity for the ER and *N*-desmethyl TAM to ENDX [5,6] (see Fig. 1). This enzyme is present in different forms in different people and some people may entirely lack it [7]. That's why not all women respond to treatment with TAM. In women with low CYP2D6 variations metabolize levels, called "poor metabolizers", TAM is too low to prevent breast cancer recurrence. The risk of breast cancer recurrence in TAM-treated women increased by background reduced CYP2D6 metabolism and low ENDX concentration.

Mutations in CYP2D6 may prevent response to TAM by preventing formation of ENDX. The gene expression patterns of five genes have been validated to be differentially regulated by ENDX and 4-HTAM. ENDX and 4-HTAM have similar effects on global gene expression patterns in MCF-7 cells and the majority of the affected genes are estrogen-regulated genes [7]. The secondary TAM metabolite, ENDX, formed stronger complexes than TAM and 4HTAM. The complexion of TAM and its metabolites induced protein unfolding. In human, ENDX plasma concentrations are typically six fold –tenfold greater than 4HTAM plasma concentration.

The activity of TAM and its metabolites depend on the drug-DNA binding mode which correlated with the action mechanism of antitumor [8]. P. Bourassa et al. demonstrated that the ENDX has the lowest free binding energy [9].TAM diffuses into the target cell, binds to estrogen receptor and translocate into the cell's nucleus where it modulates the expression of a variety of specific genes. ENDX causes the partial degradation of estrogen receptor after diffusion into the target cell [10].

The interaction of TAM and its metabolites with HSA can be used as a model for elucidating the nature of TAM binding with estrogen to gain insight into mechanism of the breast cancer therapy. A possible

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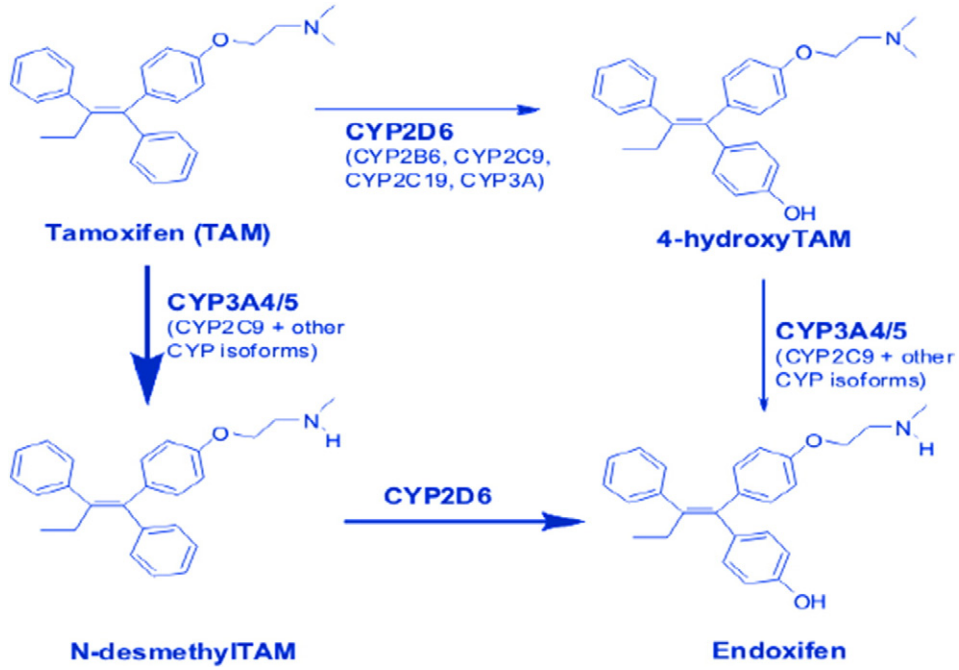

Fig. 1. Main metabolic pathway of ENDX.

mechanism could be hydrogen bond (HB) contacts with different amino acids which stabilized drug-HSA complexes. (see Fig. 2).

To anticipate the pharmacological response, desired concentration of TAM in systemic circulation should be achieve. The major challenge with the drug TAM lies with their poor bioavailability. Its bioavailability mainly depends on aqueous solubility, permeability and presystemic metabolism. TAM poor solubility and low permeability results in high doses to reach therapeutic plasma concentrations. TAM has poor aqueous solubility and slow drug absorption that lead to inadequate bioavailability and toxicity.

We suppose that physical modification of the environment can be used to enhance the solubility of the TAM. So the investigation of the stability and reactivity of Tam and its metabolites in different solvent is crucial. The main objective of this study is to investigate the detailed solvent effects on the geometrical and topological parameters and the DFT based descriptors of the TAM metabolites antitumor.

Based on solvent induced vibrational frequency shift, important information about solute-solvent interactions and chemical binding [11] could be obtained and SFS of TAM and its metabolites have been studied in the harmonic approximation at the B3LYP6/311++G(d, p) level of theory.

The study was complemented with natural bond orbital (NBO) and Atom in Molecule (AIM) analysis. Chemical reactivity indices such as ionization potential, electron affinity, chemical potential, hardness and softness are also investigated from the frontier molecular orbital analysis.

Three commonly encountered solvents are: non polar, polar protic and polar aprotic. A constant called" dielectric or permittivity" measures the polarity of a solvent hence the grater the dielectric constant, the greater the polarity. Protic solvents have O—H or N—H band that participate in a powerful intermolecular force HB, in contrast with aprotic solvents. To model the solvation effects the polarizable continuum model (PCM) which belongs to the class of continuum polarizable solvation models have been used. PCM models the solvent as a polarizable continuum rather than individual molecules and can be applied to different systems [12–16].

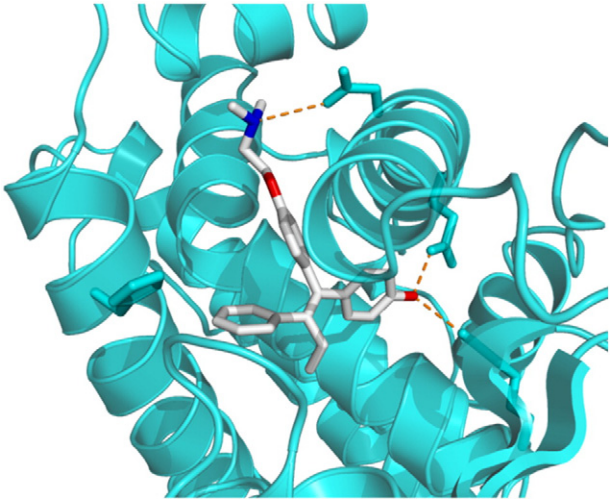

Fig. 2. Crystallographic structure of TAM metabolites.

2. Computational details

All calculations were performed at the DFT computational level by using Gaussian 09 program and Gauss View molecular visualization program package [17]. Becke's three parameter hybrids function combined with the Lee-Yang-Parr correlation functional (B3LYP) with the 6-311++G (d, p) basis set were used. PCM calculation model have been employed to study the solution-phase geometry optimization, stability and reactivity descriptors and harmonic vibrational frequencies.

A wide spectrum of solvents with dielectric constant value, ε, ranging from 2.24 to 78.40 was selected to investigate nonpolar, polar aprotic and protic solvent effects by means of DFT/B3LYP method. The value of the natural bond orbital (NBO) and Mulliken atomic charges on the atoms and orbital energies are obtained with B3LYP method in Gaussian 09 package. Harmonic vibrational frequencies and intensities for studied compounds were obtained at the same level of theory using the same basis set. Frequencies were obtained with DFT/B3LYP/6-311++G (d, p) because of its desirable performance model on the vibrational frequencies and geometries.

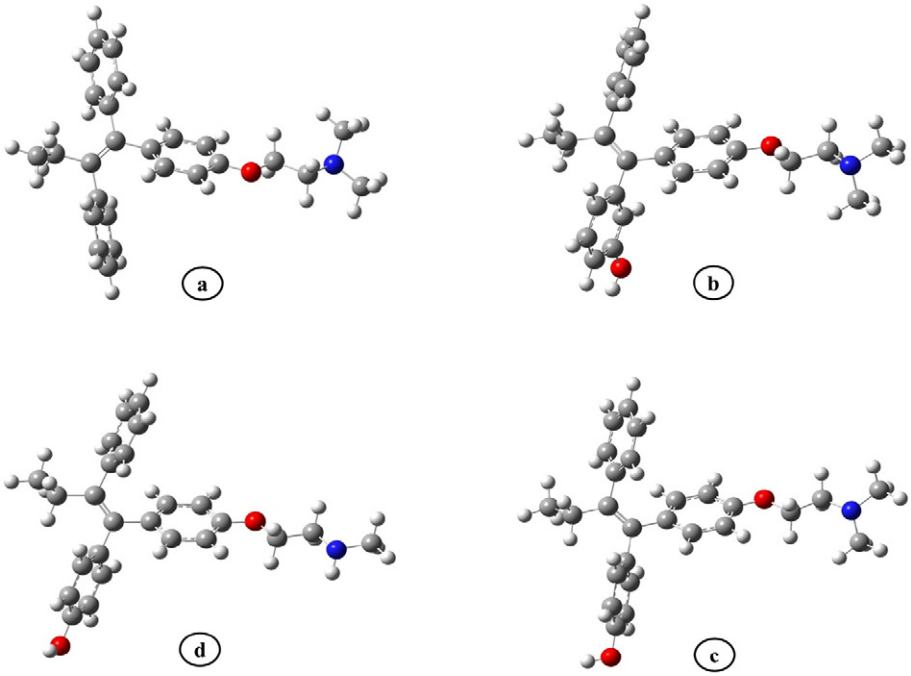

Fig. 3. The optimized structures of (a) TAM (b) 3-HTAM (c) 4-HTAM and (d) ENDX with N in blue, O in red, C in gray and H in white colors.

NBO and Mulliken charges of optimized structures were calculated using Natural population analysis. Bader's atom in molecules theory (AIM) by using the AIM2000 code is done to analyze the reactivity of compounds [18–21]. The HOMO-LUMO analysis is employed to calculate the molecular properties such as ionization potential, electron affinity, chemical potential, hardness and softness. According to Koopmans's theorem [22]:

$$\mu = \left(\frac{\partial E}{\partial N}\right)_{V(r),T} \approx \frac{\varepsilon_L + \varepsilon_H}{2} \quad (1)$$

$$\eta = \left(\frac{\partial^2 E}{\partial N^2}\right)_{V(r),T} \approx \frac{\varepsilon_L - \varepsilon_M}{2} \quad (2)$$

$$s = \frac{1}{2\eta} \quad (3)$$

Where E is the total electron energy, N is the number of electrons; V(r) is the external potential, and ε_H ε_L and s are the orbital energy of HOLO and LUMO and softness respectively. The orbital energies of HOMO and LUMO orbitals and the energy gap between them were obtained from DFT calculations.

3. Results and discussion

3.1. Molecular structure

Among the two different conformers, TAM-trans form has been studied since TAM-cis form behaved as a weak estrogen agonist without clinical usage. Fig. 3 shows the optimized molecular structure of title compound calculated at B3LYP/6-311++G (d, p) level. The calculated total energies, dipole moments and stabilization energies (E_{stab}) of the title compounds in various medium were listed in Table 1. The calculated data indicates that the total energies of molecules in solvent are lower than the gas phase. As the size of the electric permittivity of solvent increases, the stabilization energies increase. The dipole moments of molecule-solvent system increase by changing the gas phase to solvent. The calculated results at B3LYP/6-311++G (d, p) method showed that 3-HTAM has the largest dipole moment value in all solvent.

Table 1
The calculated total energies, dipole moments and stabilization energies (E_{stab}) of the title compounds in various medium.

	Tamoxifen	Droloxifen	Afimoxifen	Endoxifen
Gas phase ($\varepsilon = 1$)				
Total energy (Etot, Hartree)	−1138.4696	−1213.71696	−1213.71667	−1174.4011
Dipole moment (Debye)	1.413	2.1233	1.3119	1.6001
Carbontetra Choloride ($\varepsilon = 2.24$)				
Total energy (Etot, Hartree)	−1138.4734	−1213.7225	−1213.7222	−1174.4072
Dipole moment (Debye)	1.4931	2.3825	1.4199	1.7815
Estab (kJ/mol)	−9.98	−14.18	−14.52	−16.02
Aceton ($\varepsilon = 2.5$)				
Total energy (Etot, Hartree)	−1138.479	−1213.7302	−1213.7299	−1174.4154
Dipole moment (Debye)	1.5435	2.7452	1.6064	2.1547
Estab (kJ/mol)	−24.68	−34.76	−34.74	−37.54
Ethanol ($\varepsilon = 24.5$)				
Total energy (Etot, Hartree)	−1138.4792	−1213.7304	−1213.7301	−1174.4156
Dipole moment (Debye)	1.5438	2.7567	1.6135	2.1703
Estab (kJ/mol)	−25.21	−35.29	−35.26	−38.07
DMSO ($\varepsilon = 46.5$)				
Total energy (Etot, Hartree)	−1138.4796	−1213.7309	−1213.7306	−1174.41623
Dipole moment (Debye)	1.5443	2.784	1.6301	2.2065
Estab (kJ/mol)	−26.26	−36.60	−36.57	−39.65
Water ($\varepsilon = 78.4$)				
Total energy (Etot, Hartree)	−1138.498	−1213.7312	−1213.7309	−1174.4165
Dipole moment (Debye)	1.5446	2.7972	1.6379	2.2237
Estab (kJ/mol)	−73.51	−37.39	−37.36	−40.43

$E_{stab} = E_{in\ solvent} - E_{in\ gas}$

Table 2
Optimized geometry (bond length [B.L. in Å]) and topological parameter for studied molecules.

Environment		Tamoxifen			Droloxifen				Afimoxifen				Endoxifen				
		Lable			Lable				Lable				Lable				
		$N-C_{45}$	$N-C_{49}$	$N-C_{53}$	$N-C_{44}$	$N-C_{48}$	$N-C_{52}$	$O-C_6$	$O-H_{58}$	$N-C_{43}$	$N-C_{47}$	$N-C_{51}$	$O-C_5$	$O-H_{57}$	$N-C_{43}$	$N-C_{47}$	$N-H_{55}$	$O-C_5$	$O-H_{53}$
Gas	B.L.	1.462	1.458	1.459	1.462	1.458	1.459	1.371	0.963	1.462	1.458	1.459	1.371	0.963	1.459	1.460	1.015	1.370	0.963
	ρ	0.267	0.267	0.267	0.267	0.267	0.267	0.280	0.367	0.267	0.267	0.267	0.280	0.367	0.267	0.265	0.339	0.280	0.367
	$\nabla^2\rho$	−0.696	−0.701	−0.699	−0.696	−0.701	−0.699	−0.372	−2.531	−0.696	−0.701	−0.699	−0.368	−2.531	−0.703	−0.691	−1.481	−0.365	−2.532
CCl_4	B.L.	1.462	1.460	1.461	1.462	1.460	1.461	1.371	0.964	1.462	1.460	1.461	1.371	0.964	1.460	1.462	1.015	1.371	0.964
	ρ	0.267	0.266	0.266	0.267	0.266	0.266	0.280	0.365	0.267	0.266	0.266	0.280	0.365	0.267	0.264	0.339	0.280	0.365
	$\nabla^2\rho$	−0.693	−0.696	−0.694	−0.693	−0.696	−0.695	−0.373	−2.539	−0.693	−0.696	−0.694	−0.369	−2.539	−0.699	−0.686	−1.491	−0.368	−2.540
Acetone	B.L.	1.463	1.462	1.463	1.463	1.462	1.463	1.371	0.965	1.463	1.462	1.463	1.372	0.965	1.462	1.464	1.016	1.371	0.965
	ρ	0.267	0.265	0.265	0.267	0.265	0.265	0.280	0.363	0.267	0.265	0.265	0.279	0.363	0.267	0.262	0.339	0.280	0.363
	$\nabla^2\rho$	−0.691	−0.690	−0.688	−0.690	−0.690	−0.688	−0.374	−2.548	−0.691	−0.690	−0.688	−0.371	−2.548	−0.696	−0.681	−1.505	−0.370	−2.548
Ethanol	B.L.	1.463	1.462	1.463	1.463	1.462	1.463	1.371	0.965	1.463	1.462	1.463	1.372	0.965	1.462	1.464	1.016	1.371	0.965
	ρ	0.267	0.265	0.265	0.267	0.265	0.265	0.280	0.363	0.267	0.265	0.265	0.279	0.363	0.267	0.262	0.339	0.280	0.363
	$\nabla^2\rho$	−0.691	−0.690	−0.688	−0.690	−0.690	−0.688	−0.374	−2.549	−0.691	−0.690	−0.687	−0.371	−2.548	−0.695	−0.680	−1.506	−0.370	−2.548
DMSO	B.L.	1.463	1.462	1.463	1.463	1.462	1.463	1.372	0.965	1.463	1.462	1.463	1.372	0.965	1.462	1.464	1.016	1.371	0.965
	ρ	0.267	0.265	0.265	0.267	0.265	0.265	0.280	0.363	0.267	0.265	0.265	0.279	0.363	0.267	0.262	0.339	0.280	0.363
	$\nabla^2\rho$	−0.690	−0.690	−0.687	−0.690	−0.690	−0.688	−0.375	−2.549	−0.690	−0.690	−0.687	−0.371	−2.549	−0.695	−0.680	−1.507	−0.370	−2.549
Water	B.L.	1.463	1.462	1.463	1.463	1.462	1.463	1.372	0.965	1.463	1.462	1.463	1.372	0.965	1.462	1.464	1.016	1.371	0.965
	ρ	0.267	0.265	0.265	0.267	0.265	0.265	0.280	0.363	0.267	0.265	0.265	0.279	0.365	0.267	0.262	0.339	0.280	0.363
	$\nabla^2\rho$	−0.690	−0.689	−0.687	−0.690	−0.690	−0.069	−0.375	−2.549	−0.690	−0.689	−0.687	−0.369	−2.507	−0.695	−0.680	−1.508	−0.371	−2.549

The total energies shift to lower value with the increasing electric permittivity of the solvent. TAM has the highest stabilization energy value with $E_{stab} = -73.51$ kJ/mol in water medium thus it has the most stable systems of molecule-solvent. Optimized bond length of the most preferred drug binding sites of these antitumor compounds [10] listed in Table 2. These geometries in solution are slightly different from of the gas phase. The O—H bond length in studied compounds increases with increasing solvent polarity, so the condition for HB formation in water polar protic solvent is most favorable (Fig. 4).

3.2. AIM analysis

The quantum theory of atoms in molecule (QTAIM) formalism which characterized the bonds through a topological analysis of electronic charge density, ρ_{BCP}, and their Laplacian ($\nabla^2\rho_{BCP}$) at the bond critical point (BCP) were performed. Region of concentration of electron charge density which classified the atomic interaction within shared interaction ($\nabla^2\rho_{BCP} < 0$) and closed shell interaction ($\nabla^2\rho_{BCP} > 0$) have been determined [23,24]. The calculated largest ρ_{BCP} in gas phase shows that the hydrogen bond strength in solution is weaker when compared to the gas phase.

The positive value of charge density for the N—C, N—H and O—H bond critical points are relatively high and the $\nabla^2\rho_{BCP}$ is negative values which decrease from gas phase to polar protic solvent. As the proton donor is more important than proton acceptor in hydrogen bond formation, bond elongation and weakening in donor-H bond upon complexion are important features of hydrogen bond. Results show that the O—H bond length of the studied compounds is longer in the polar solvents.

3.3. Natural population analysis

The calculated values of natural bond orbitals (NBO) and Muliken charges on oxygen and nitrogen heteroatoms of optimized geometries in various medium based on theory of natural population analysis are given in Table 3.

The results show an increase of negative NBO and Muliken charges on oxygen atom with going from polar aprotic to polar protic solvents and the highest atomic charge in water medium, candidate O to participate in hydrogen bond formation (see Fig. 5). The order of atomic charge on O atom in all solvents of title molecules is 4-HTAM > ENDX > 3-HTAM so more positive charge on H atom cause stronger inter-molecular HB.

Although at first glance the tendency of solvent effect on NBO negative charge on N atom in TAM, 3HTAM and 4HTAM compounds are similar to O atom from gas phase to more polar solvents, but positive Muliken charge on N decreases in the direction of gas → CCl_4 → acetone → Ethanol → DMSO, ENDX negative Muliken charge however, increase in solvents with the increase of electric permittivity. Oxygen and Nitrogen atoms, take the most negative charges in water polar protic solvent. These changes reflect large effect of polar solvents on molecules.

3.4. Frontier molecular orbital analysis

The frontier orbitals, the highest occupied molecular orbital (HOMO) and the lower unoccupied molecular orbital (LUMO), analysis are performed to evaluate the chemical stability and binding scheme of studied antitumor compounds. The HOMO represents the ability to donate an electron and LUMO as electron acceptor represents the ability to obtain electron. HOMO-LUMO energy calculations are carried out by B3LYP/6-311++G (d, p). The energy gap between HOMOs and LUMOs as a stability index is calculated [25,26]. The energy of the frontier molecular orbitals HOMO and LUMO, Eg, chemical potential, hardness and softness index for the title compound calculated at B3LYP/6-31G(d, p) level are listed in Table 4. As can be seen in this Table, the

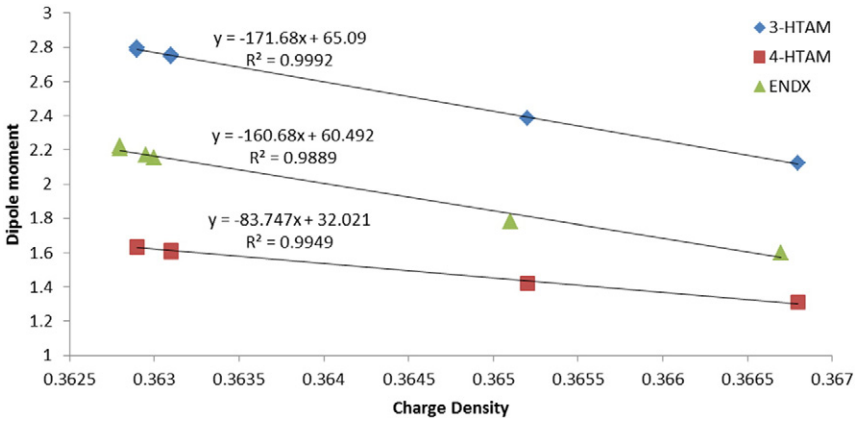

Fig. 4. A plot of O—H charge density Vs. Dipole moment.

Table 3
The calculated NBO and Mulliken atomic charges on oxygen and nitrogen atoms for title molecules.

		Atomic charges on oxygen atom		Atomic charges on nitrogen atom	
Complex	Environment	NBO	Mulliken	NBO	Mulliken
Tamoxifen	Gas	–	–	−0.5604	0.1338
	CCl_4	–	–	−0.5634	0.1006
	Acetone	–	–	−0.5688	0.0481
	Ethanol	–	–	−0.5688	0.0481
	DMSO	–	–	−0.5687	0.0480
	Water	–	–	−0.5688	0.0479
Droloxifen	Gas	−0.6734	−0.2173	−0.5622	0.1351
	CCl_4	−0.6829	−0.2404	−0.5643	0.1019
	Acetone	−0.6942	−0.2664	−0.5690	0.0568
	Ethanol	−0.6946	−0.2671	−0.5691	0.0556
	DMSO	−0.6953	−0.2687	−0.5695	0.0527
	Water	−0.6956	−0.2694	−0.5696	0.0514
Afimoxifen	gas	−0.6750	−0.2334	−0.5612	0.1329
	CCl_4	−0.6846	−0.2553	−0.5642	1.0006
	Acetone	−0.6958	−0.2798	−0.5691	0.0525
	Ethanol	−0.6961	−0.2804	−0.5692	0.0511
	DMSO	−0.6968	−0.2819	−0.5696	0.0479
	Water	−0.6971	−0.2825	−0.5698	0.0463
Endoxifen	Gas	−0.6746	−0.2328	−0.675	−0.0979
	CCl_4	−0.6839	−0.2546	−0.6816	−0.1301
	Acetone	−0.6946	−0.2794	−0.6916	−0.1729
	Ethanol	−0.6949	−0.2801	−0.6919	−0.1742
	DMSO	−0.6956	−0.2816	−0.6925	−0.1771
	Water	−0.6959	−0.2823	−0.6928	−0.1784

relatively high value of energy gap indicates that the title compounds presents high chemical stability and thus low reactivity from gas phase to water.

Furthermore the order of energy gap of studied molecules in gas phase is 3-HTAM < 4-HTAM < TAM < ENDX. In other solvents the following order is found:

ENDX < 4-HTAM < 3-HTAM < TAM.

As expected ENDX has the lower energy gap so the eventual charge transfer interactions would rather take place within this antitumor and enhance its bioactivity in target cells.

The calculated chemical potential is negative which indicate that the compounds are stable. As the size of the electric permittivity of solvent increases, chemical reactivity indices of the title compounds such as, ionization potential, electron affinity and hardness increases. Considering the chemical softness in water medium the order, ENDX > 4-HTAM > 3-HTAM ≥ TAM can be seen so ENDX is the most chemical reactive molecule in that solvent. Moreover, in this study, the softness of the molecules increases by decrease of HOMO-LUMO energy gap with the following equation.

$$s = -0.0426E_{HOMO\text{-}LUMO} + 0.4129 \quad (4)$$

3.5. Vibrational analysis

Besides the molecular structure, the environmental factors such as solvent, temperature, pressure and different molecules in medium affect the normal mode vibrational frequencies. Frequency calculations in the harmonic approximation are also performed with the same basis set and since no imaginary frequencies were found, the optimized structures correspond to the energy minima.

Table 5 indicates effective effects on the solvent-induced stretching vibrational frequency shifts (SFS). Symmetric stretching vibrations of O—H bond shifts to lower frequencies from gas phase to acetone (larger

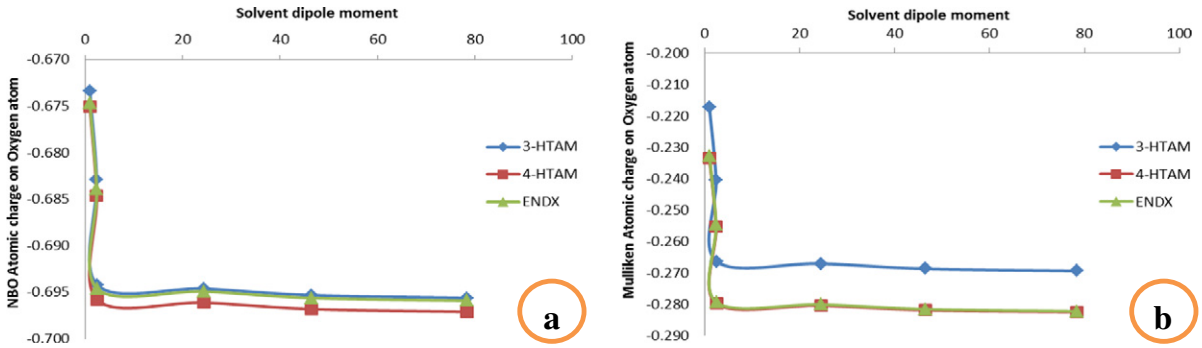

Fig. 5. The calculated NBO and Mulliken atomic charges on Oxygen and Nitrogen atoms for title molecules.

Table 4
Frontier molecular orbital energies, HOMO-LUMO gap and reactivity descriptors for studied antitumors calculated at B3LYP/G(d,p) level.

	Tamoxifen						Droloxifen					
Molecular parameters	Gas	CCl_4	Acetone	Ethanol	DMSO	Water	Gas	CCl_4	Acetone	Ethanol	DMSO	Water
E_{HOMO} (eV)	−5.667	−5.750	−5.909	−5.914	−5.926	−5.932	−5.647	−5.734	−5.911	−5.917	−5.932	−5.938
E_{LUMO} (eV)	−0.887	−0.926	−0.992	−0.994	−0.999	−1.001	−0.889	−0.936	−0.997	−0.999	−1.004	-1.007
E_{HOMO}-E_{LUMO} (eV)	4.781	4.825	4.917	4.920	4.927	4.931	4.758	4.798	4.913	4.918	4.928	4.931
Ionization potential, IP (eV)	5.667	5.750	5.909	5.914	5.926	5.932	5.647	5.734	5.911	5.917	5.932	5.938
Electron affinity, EA (eV)	0.887	0.926	0.992	0.994	0.999	1.001	0.889	0.936	0.997	0.999	1.004	1.007
Chemical hardness, η (eV)	2.390	2.412	2.458	2.460	2.464	2.465	2.379	2.399	2.457	2.459	2.464	2.466
Chemical softness, s (eV^{-1})	0.209	0.207	0.203	0.203	0.203	0.203	0.210	0.208	0.204	0.203	0.203	0.203
Chemical potential, μ (eV)	−3.277	−3.338	−3.450	−3.454	−3.462	−3.466	−3.268	−3.335	−3.335	−3.458	−3.468	−3.473
	Afimoxifen						Endoxifen					
Molecular parameters	Gas	CCl_4	Acetone	Ethanol	DMSO	Water	Gas	CCl_4	Acetone	Ethanol	DMSO	Water
E_{HOMO} (eV)	−5.609	−5.690	−5.841	−5.847	−5.859	−5.865	−5.650	−5.660	−5.805	−5.805	−5.817	−5.823
E_{LUMO} (eV)	−0.841	−0.882	−0.954	−0.956	−0.966	−0.963	−0.838	−0.884	−0.949	−0.951	−0.954	−0.956
E_{HOMO}-E_{LUMO}, Eg (eV)	4.768	4.808	4.887	4.890	4.893	4.901	4.812	4.776	4.857	4.855	4.863	4.867
Ionization Potential, IP (eV)	5.609	5.690	5.841	5.847	5.859	5.865	5.650	5.660	5.805	5.805	5.817	5.823
Electron affinity, EA (eV)	0.841	0.882	0.954	0.956	0.966	0.963	0.838	0.884	0.949	0.951	0.954	0.956
Chemical hardness, η (eV)	2.384	2.404	2.444	2.445	2.447	2.451	2.406	2.388	2.428	2.427	2.432	2.434
Chemical softness, s (eV^{-1})	0.210	0.208	0.205	0.205	0.204	0.204	0.208	0.209	0.206	0.206	0.206	0.205
Chemical potential, μ (eV)	−3.225	−3.286	−3.398	−3.401	−3.413	−3.414	−3.244	−3.272	−3.377	−3.378	−3.386	−3.389

than 10 cm^{-1}) while smaller shifts occur in more polar solvents. Less noticeable N—C and N—H bond blue shift to lower values with the increasing solvent polarity can be seen in the results. The presence of dielectric medium changes the corresponding IR intensities with the increasing solvent polarity more than the frequencies. It is obvious that the frequencies of vibrational modes are not only depends on molecular geometry but also affected by environmental factors. According to O—H stretching vibrations shifts to lower frequency value with increasing solvent polarity and higher electronic charge densities correspond to bond elongating which interpreted as intramolecular charge transfer in solvents. Therefore we can conclude that HB formation in polar protic solvent is achieved easier.

Table 5
Comparison of the calculated stretching vibrations and IR intensities (IIR) of studied compounds in various medium.

		Stretching vibration ν(O—H)		Stretching vibration ν(N—C)		Stretching vibration ν(N—H)	
Complex	Environment	Freq	IIR	Freq	IIR	Freq	IIR
Tamoxifen	Gas	–	–	1299.92	33.10	–	–
	CCl4	–	–	1297.07	35.41	–	–
	Acetone	–	–	1293.68	34.39	–	–
	Ethanol	–	–	1293.60	34.28	–	–
	DMSO	–	–	1293.40	34.01	–	–
	Water	–	–	1293.31	33.88	–	–
Droloxifen	Gas	3835.80	75.40	1299.63	25.03	–	–
	CCl4	3827.24	101.84	1297.02	27.59	–	–
	Acetone	3815.10	133.50	1294.12	28.19	–	–
	Ethanol	3814.68	134.82	1293.07	28.19	–	–
	DMSO	3813.89	136.18	1293.83	28.17	–	–
	Water	3813.48	137.70	1293.74	28.16	–	–
Afimoxifen	Gas	3835.99	75.16	1299.69	32.40	–	–
	CCl4	3828.13	102.02	1296.74	34.95	–	–
	Acetone	3816.48	136.27	1293.49	34.45	–	–
	Ethanol	3816.08	137.29	1293.39	34.38	–	–
	DMSO	3815.18	139.62	1293.19	34.15	–	–
	Water	3814.75	140.69	1293.10	34.03	–	–
Endoxifen	Gas	3835.63	79.88	1176.67	20.39	3513.00	0.19
	CCl4	3825.83	107.44	1174.68	16.12	3509.78	0.49
	Acetone	3814.26	143.54	1134.95	63.38	3506.29	1.33
	Ethanol	3814.12	144.67	1134.52	63.23	3506.35	1.35
	DMSO	3813.42	142.23	1173.55	11.10	3506.59	1.41
	Water	3813.07	148.43	1134.52	62.77	3506.75	1.44

4. Conclusion

The solvent effect on geometry, charge distribution, dipole moment, chemical reactivity indices and vibrational frequencies of TAM antitumor metabolites are presented via DFT/PCM calculation at B3LYP/6-311++G(d, p) level. The geometry, electronic structure, energies and stretching vibrational frequencies change with the increasing polarity of solvent. The stabilization energy and dipole moment of the title molecules increase with increasing electro permittivity of solvents. Solvent effect induced slight changes in geometry of the studied compounds. As the interaction of present antitumor with HAS is via HB, so the solvent-molecule interactions around the oxygen atom are more important. The results show that atomic charge on O atom increases with increasing of solvent permittivity so the O—H bond length and stretching vibrational values shift to lower values and HB formation is more favorable. As the energy gap of frontier molecular orbitals increases, the softness decreases and thus the reactivity of molecules decreases. The changes in ENDX metabolite of TAM are interpreted as result of more stability of this compound in water medium and stronger HB interaction to target molecules. Our results elucidate the higher stability and lower reactivity of the ENDX in water medium so it's necessary to apply drug carrier systems with good aqueous solubility to improve the bioavailability of these antitumor drugs in cancer therapy.

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